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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,788	01/23/2002	James Allen	AVIGEN.004A	9362

35735 7590 07/02/2004

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,788	ALLEN, JAMES	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 1-21 are pending examination.

Applicants traversal, the amendment to claims 1, 3, 12, 13, 14 and the addition of claims 16-21 in paper filed on 5/6/04 is acknowledged and considered.

Election/Restrictions

Claims 5 and 6 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/27/03.

Claim Objections

Claim 1 is objected to because of the following informalities: The term "expression" on line 4 in claim 1 is now misspelled. The term was amended in paper filed on 5/6/04 with no markings to indicate the change. In response to the instant action, applicants should come in with markings of the term in claim 1 to indicate the change.

In the response to this instant office action, applicants are reminded to follow revised 37 CFR 1.121. See 68 Fed. Reg. 38611 (June 30, 2003) or website http://www.uspto.gov/web/patents/ifw/.

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 recites "by way of administration to said muscle cell," which is already recited in the claim from which it depends.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 3, 4, and 7-15 remain and claims 16-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hemophilia in a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid encoding a factor IX protein operably linked to expression control elements is directly administered to at least one muscle cell in the mammal, does not reasonably provide enablement for a method of gene therapy comprising administering at least one rAAV comprising an AAV-6 capsid and a heterologous nucleic acid operably linked to expression control elements to at least one muscle cell using a genus of administration routes, whereby expression of said nucleic acid provides for a therapeutic effect. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence

or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is directed to using a rAAV virion comprising an AAV-6 capsid in a method of gene therapy for treating any disease and/or disorder in a mammalian subject. More specifically, the invention is directed to the rAAV virion for treating blood coagulation disorders in a mammalian subject by administering the rAAV virion to muscle cells of the mammalian subject. The invention lies in the field of gene therapy.

Furthermore, and with respect to claims directed to any gene therapy directed to any treatment of a mammal; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Therefore, at the time the application was filed, gene therapy was considered unpredictable.

The specification contemplates using rAAV-6 virion comprising a heterologous nucleic acid (HNA) to treat a variety of disorders and/or diseases in a mammal by administering the rAAV-6 virion to muscle cells of said mammal (see pages 10-12). The delivery of rAAV-6 to muscle cells may be by intramuscular injection or by administration into the bloodstream. The specification teaches production of a recombinant AAV factor IX virion (Example 1, pages 16-19). The specification teaches administration of said virion to RAG-1 female immunodeficient mice (pages 19-20). The specification teaches treating hemophilia B dogs having hemophilia B using said virion (Example 3, pages 20-21). The specification contemplates hemophilia B treatment in humans with AAV6-human factor IX (page 21).

The specification provides sufficient guidance and/or factual evidence for treating hemophilia B in a mammal using rAAV-6 virion comprising a HNA encoding a factor IX protein operably linked to expression control elements. However, in view of the In Re Wands Factors, the as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to use the full scope of the claimed invention. The breadth of the claimed methods embraces treating a variety of diseases and/or disorders (see pages 10-12) in a mammalian subject using rAAV-6 virion that are not taught by the prior art or the as-filed specification.

The art of record teaches several problems with gene therapy (See Rubanyi, Molecular Aspects of Medicine, Vol. 22, 2001, pages 113-142, Orkin et al., "Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy" December 7, 1995, Anderson, *supra* and Verma, *supra*).

The claimed methods recite using any route of delivery for providing said rAAV virion to muscle cells in vivo to produce a therapeutic effect. The specification teaches using intramuscular (i.m.) administration for targeting muscle cells. However, the art of record and the specification do not teach how to use any other route of administration to target said muscle cells and provide a therapeutic effect. Monahan teaches rAAV are able to transduce a wide range of tissue types leading to gene expression several types (Molecular Medicine Today, Vol. 6, pages 433-440, 2000). Since rAAV can transduce several different types of cells in a mammal, the specification does not teach one skilled in the art how to sufficiently target enough rAAV to the muscle using any route of administration other than i.m. to produce gene expression at a therapeutic level in the muscle. In addition, treating each disease and/or disorder contemplated

by the specification with the claimed method would require a certain amount of gene expression in a particular organ or tissue of the mammal. For example, some lysosomal disorders result from lack of expression of an enzyme in several tissues including the brain (e.g., Fabry disease). The specification does not teach how to express the HNA at a therapeutic effect in the brain of a mammal with the lysosomal disorder by expressing the HNA in the muscle of the mammal. The specification does not provide sufficient guidance for how to reasonably extrapolate from treating hemophilia B using i.m. injection of AAV6 virion to a method of treating any disease or disorder using any other route of administration to provide a therapeutic effect in the muscle cells for a disease and/or disorder.

In addition, with respect to using AAV6 to treat any disease or disorder contemplated by the specification, it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of gene therapy, for those skilled in

the art to experiment with level of HNA expression so as to provide a therapeutic effect as intended by the as-filed specification at the time the invention was made.

See also Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification for treating a disease and/or disorder using the claimed method; the specification does not provide reasonable detail for what protocols are required for different methods of gene therapy, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed methods.

In addition, the art of record teaches problems with using rAAV in gene therapy (Monahan, *supra* and Hortelano et al., Art. Cells, Blood, Subs., and Immod. Biotech. Vol. 28, pages 1-24, 2000, and Wang et al., PNAS, Vol. 97, pages 13714-13719, 2000). The genome of AAV is only 4.7kb-5.0kb, which is too short to use for delivering some nucleic acid sequences, e.g., full-size of hFVIII cDNA, CFTR, and the dystrophin gene. Hortelano teaches, "Despite the promising results obtained with AAV vectors delivering FIX, it has not yet been used to deliver FVIII (page 10)." Wang teaches, "AAV are too small (5kb) to package the 14-kb dystrophin cDNA (page 13714)." The specification does not teach one skilled in the art how to overcome the size limitation of AAV vectors. The specification does not provide sufficient guidance and/or factual evidence to the art used to overcome the problems with AAV size limitation.

Furthermore, claim 15 recites increasing blood-clotting efficiency in said mammalian subject using a HNA. The specification and art of record do not provide sufficient guidance to use any HNA other than blood coagulation factors (e.g., Factor IX) to increase blood-clotting efficiency in said mammalian subject. However, the relevance of this data to using a genus of HNAs to increase blood-clotting efficiency is unclear at best because neither the applicant nor the prior art provide a correlation or nexus between the results obtained for Factor IX using AAV6 in the specification to using a genus of HNAs, which the skilled artisan would reasonably expect to see increase blood-clotting efficiency.

In view of the In Re Wands Factors, it would take one skilled in the art an undue amount of experimentation to practice the full breadth of the claimed invention. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed methods generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any gene therapy method as contemplated by the claims, particularly given the unpredictability of gene therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the for a method of treating hemophilia in a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid encoding a factor IX protein operably linked to expression control elements is directly administered to at least one muscle cell in the mammal and not for the full breadth of the claimed methods. Given that gene therapy wherein any rAAV is employed to correct a disease or a medical condition in any

mammalian subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any rAAV virion cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 5/6/04 have been fully considered but they are not persuasive.

Applicants argue that the specification clearly described and enabled any route of delivery of rAAV to target muscle cells. The argument is not found persuasive because in view of the In Re Wands Factors, the as-filed specification does not provide sufficient guidance use a genus of administration routes to target said muscle cells and provide a therapeutic effect. Furthermore with respect to applicants citing parts of the specification (page 5, lines 16-18 and page 12-13) to support their argument, it appears that applicants are arguing against a written description rejection and not an enablement rejection for the route of delivery of rAAV. The pages cited by the applicants, recite different methods of delivering rAAV to muscle cells and do not teach one skilled in the art how to administer a sufficient amount of rAAV using a genus of administration routes to observe a therapeutic effect. As stated above, since rAAV can transduce several different types of cells in a mammal, the specification does not teach one skilled in the art how to sufficiently target enough rAAV to the muscle using a genus of administrations routes other than direct administration to the muscle to produce gene expression at a therapeutic level in the muscle.

With respect to applicants' argument that a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance, with respect to the direction in which the experiment should proceed, to enable the determination of how to practice a desired embodiment of the claimed invention (Ex parte Forman, 230 USPQ 546 (BPAI 1986) and In Re Wands, supra), the argument is not found persuasive because the specification must be enabling as of the filing date. See MPEP 2164.05(a). Given the above analysis of the In Re Wands Factors, it is concluded that the skilled artisan would have need to have concluded undue and excessive experimentation in order to practice the full scope of the claimed invention.

In addition, In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states:

> Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements, while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The applicants teach treating hemophilia B in a mammal using rAAV-6 virion comprising a HNA encoding a factor IX protein operably linked to expression control elements using i.m. administration to muscle cells. However, the relevance of this data to treatment of any other disease and/or disorder using the claimed method is unclear at best because neither the applicants nor the prior art provide a correlation or nexus between the results obtained in the specification

such as those provided by applicants with results which the skilled artisan would reasonable expect to see in any other gene therapy. See Juengst, BMJ, 326:1410-1, 2003.

With respect to applicants' argument that applicant is not required to prove operability of each embodiment (See MPEP 2164.08(B)) and the specification need not teach what is well known in the art (Hybridtech Inc. v. Monoclonal Antibodies, Inc. 231 USPQ 81, 94 (Fed. Cir. 1986), the argument is not found persuasive because the breadth of the claims encompasses using rAAV6 in any gene therapy method comprising administering said rAAV6 to at least one muscle and observing a therapeutic effect and the specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to determine without undue and excessive experimentation which gene therapy methods can be used in the claimed invention. Furthermore, the assertion by applicants that using rAAV6 to treat any diseases in a mammal is well known in the art is not supported by any evidence of record. See MPEP § 716.01(c).

With respect to the articles cited by applicants for support of the claimed invention, the articles do not support practicing the full breadth of the claimed invention because nothing in the specification directs a skilled artisan to methods and materials in the pre-filing articles or the post-filing art. With respect to the post-filing articles, the specification must be enabling as of the filing date (See MPEP 2164.05(a)) and the specification fails to provide sufficient guidance and/or factual evidence that the methods taught in the post-filing articles were considered enabled at the time the application was filed. The argument with respect to the articles is moot because the articles used different methods and materials that are not taught in the as-filed specification. While, it is acknowledged that other types of gene therapies have been cited in the prior art as treating a particular disease or genetic disorder using distinct material and methods,

the art of record teaches that one skilled in the art can not reasonably extrapolate from one type of gene therapy to another type of gene therapy without an undue amount of experimentation and the art of record teaches that there is no universal protocol that can be reasonably extrapolated from one type of gene therapy to the claimed gene therapy method (See Verma, Anderson, Orkin, and Rubanyi).

With respect to applicants' argument that one skilled in the art could readily determine, in view of the state of the art and the teachings of applicant's specification, how to select and use suitable nucleotide sequences for a given disease, the argument is not found persuasive because the argument is not supported by any evidence of record. See MPEP § 716.01(c) and In Re Fisher, supra.

With respect to applicants' argument that the specification is enabled for delivering any blood coagulation factor (e.g., Factor IX) to increase blood-clotting efficiency (see specification, page 12), the argument is not found persuasive because the breadth of the claims not only embraces blood coagulation factors, but other heterologous nucleic acids that are not considered enabled for increasing blood clotting efficiency. In view of the art of record, Applicants do not demonstrate that the method taught in the specification correlates to practicing the full breadth of the claimed method to increase blood-clotting efficiency in a mammal. The applicants do not teach a skilled artisan how to use Factor VIII in an AAV-6 since the prior art teaches that AAV is too small to package the gene encoding Factor VIII. Furthermore, with respect to the applicants citing page 12 of the specification to support their argument, it appears that applicants are arguing against a written description rejection and not an enablement rejection for using a genus of HNA to increase blood-clotting efficiency. The page cited by the applicants, recites

what types of factors could be used in the claimed, however, nothing on this page provides a correlation or nexus between the results obtained in the working examples of the specification with results which the skilled artisan would reasonably expect to see using a genus of HNA to increase blood-clotting efficiency embraced by the claimed method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 16 is rejected under 35 U.S.C. 102(e) as being anticipated by Li (US 2002/0177222). Li teaches production of wild type free recombinant AAV virions (rAAV) (pages 2-3 and 5). Li teaches using rAAV6 to deliver genetic material into a human to cure a genetic defect or to effect a desired treatment (pages 3 and 5).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 4, 7, 8, 10, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al., (US Patent 6,156,303) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945).

Russell teaches using AAV6 comprising a nucleic acid sequence to treat pathologic conditions in a mammal, including blood-clotting disorders (abstract, columns 2-3, column 17, and column 72). Russell teaches delivering AAV6 vectors to muscle cells (column 27, lines 1-15 and column 72). However, Russell does not specifically teach using recombinant adeno-associated virus virions (rAAV), wherein said rAAV virions are free of helper virus.

However, at the time the invention was made, Matsushita teaches that adeno-associated virus vectors can be efficiently produced without helper virus (Gene Therapy (1998) 5, 938-945). Matsushita teaches that elimination of helper virus from the AAV vector production protocol results in a less complicated large-scale production procedure and a safer preparation of AAV virions with higher purity (page 939).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Russell taken with Matsushita to make and use a rAAV virions, free of helper virus in a gene therapy method for treating blood-clotting disorders in a mammal. One of ordinary skill in the art would have been motivated to make and use rAAV virions free of helper virus because free production of AAV vectors results in a safer preparation of AAV vectors and a less complicated large-scale production of AAV vectors.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 2, 3, 4, 7, 8, 9, 10, 11, and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over High et al., (IDS, US Patent 6,093,392) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945).

High teaches a method of treating hemophilia in a mammal comprising administering rAAV comprising a nucleic acid encoding Factor IX operably linked to an expression control element to a muscle tissue of the mammal (columns 29-30). Factor IX is a human Factor IX (column 29). High teaches that any suitable AAV vector can be used in the method, including AAV1, AAV3, AAV4, and AAV6 (column 11, lines 52-57). Furthermore, High teaches

targeting the skeletal muscle using the method (columns 25-26). However, High does not specifically teach using recombinant adeno-associated virus virions (rAAV), wherein said rAAV virions are free of helper virus.

However, at the time the invention was made, Matsushita teaches that adeno-associated virus vectors can be efficiently produced without helper virus (Gene Therapy (1998) 5, 938-945). Matsushita teaches that elimination of helper virus from the AAV vector production protocol results in a less complicated large-scale production procedure and a safer preparation of AAV virions with higher purity (page 939).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of High taken with Matsushita to make and use a rAAV virions, free of helper virus in a gene therapy method for treating hemophilia in a mammal. One of ordinary skill in the art would have been motivated to make and use rAAV virions free of helper virus because free production of AAV vectors results in a safer preparation of AAV vectors and a less complicated large-scale production of AAV vectors.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If a copy of a provisional application listed on the bottom portion of the accompanying Notice of References Cited (PTO-892) form is not included with this Office action and the PTO-892 has been annotated to indicate that the copy was not readily available, it is because the copy could not be readily obtained when the Office action was mailed. Should applicant desire a copy of such a provisional application, applicant should promptly request the copy from the Office of Public Records (OPR) in accordance with 37 CFR 1.14(a)(1)(iv), paying the required fee under 37 CFR 1.19(b)(1). If a copy is ordered from OPR, the shortened statutory period for reply to this Office action will not be reset under MPEP § 710.06 unless applicant can demonstrate a substantial delay by the Office in fulfilling the order for the copy of the provisional application. Where the applicant has been notified on the PTO-892 that a copy of the provisional application is not readily available, the provision of MPEP § 707.05(a) that a copy of the cited reference will be automatically furnished without charge does not apply.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER